General

Guideline Title

Empagliflozin in combination therapy for treating type 2 diabetes.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Empagliflozin in combination therapy for treating type 2 diabetes. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 44 p. (Technology appraisal guidance; no. 336).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:

- A sulfonylurea is contraindicated or not tolerated, or
- The person is at significant risk of hypoglycaemia or its consequences

Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- Metformin and a sulfonylurea or
- Metformin and a thiazolidinedione

Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

People currently receiving treatment initiated within the National Health Service (NHS) with empagliflozin that is not recommended for them by National Institute for Health and Care Excellence (NICE) in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Type 2 diabetes

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of empagliflozin in combination therapy for treating type 2 diabetes

Target Population

Patients with type 2 diabetes

Interventions and Practices Considered

1. Empagliflozin in a dual therapy regimen in combination with metformin
2. Empagliflozin in a triple therapy regimen with:
    - Metformin and a sulfonylurea
    - Metformin and a thiazolidinedione
3. Empagliflozin in combination with insulin with or without other antidiabetic drugs

Major Outcomes Considered

- Clinical effectiveness
    - Change in mean glycosylated haemoglobin (HbA1c) level
    - Change in body weight

    - Change in systolic blood pressure (SBP)
    - Health-related quality of life
    - Adverse events of treatment
- Cost effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission (MS) on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by Warwick Evidence (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Appendix 2 in the MS (see the "Availability of Companion Documents" field) provides detailed information on search strategies.

The ERG does not consider that any important trials of empagliflozin, dapagliflozin or canagliflozin in type 2 diabetes mellitus have been omitted.

Number of Source Documents

Clinical Effectiveness

The manufacturer included evidence on empagliflozin from eight trials, and one extension study that recruited patients from three trials. Four trials of empagliflozin are most relevant to the decision problem (see Table 1 in the Evidence Review Group [ERG] report [see the "Availability of Companion Documents" field]). See Figure 3 in the manufacturer's submission (MS) for additional information.

Cost-effectiveness

The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission (MS) on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this appraisal was prepared by Warwick Evidence (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Summary and Critique of Submitted Clinical Effectiveness Evidence

Quality of Included Randomised Controlled Trials (RCTs)

The ERG has used the Cochrane risk of bias tool to assess the quality of the included studies, and considers all trials to be of good quality (see Appendix 1 in the ERG report).

Network Meta-analysis

In absence of head to head comparisons of different flozins, the manufacturer undertook network meta-analysis (NMA). The manufacturer undertook this analysis to assess the effectiveness of empagliflozin as dual therapy with metformin, as triple therapy with metformin and sulfonylurea (SU), as triple therapy with metformin and thiazolidinedione (TZD) and finally, as an add-on to insulin. The main comparators were dapagliflozin 10 mg, canagliflozin 100 mg, canagliflozin 300 mg and sitagliptin 100 mg. However, in their network diagrams and tables, the manufacturer also reported studies related to other gliptins.

The manufacturer reported doing systematic searches to identify all the relevant studies. The outcomes analysed were change in glycosylated hemoglobin (HbA1c) from baseline, change in systolic blood pressure (SBP) from baseline, change in body weight from baseline and safety which included hypoglycaemia (non-severe), hypoglycaemia (severe), urinary tract infections (UTIs), and genital infections. The outcomes were compared at two time periods 24 ± 4 weeks and 52 ± 4 weeks.

Summary of the Manufacturer NMA Results

The relevant data from NMAs for key outcomes (change in HbA1c, body weight and SBP) in the comparisons of interest (empagliflozin versus canagliflozin, dapagliflozin and sitagliptin) in dual, triple and insulin add on therapies have been summarised in Figure 11, Figure 12 and Figure 13.

Table 14 and Table 15 in the ERG report show the ERG's critical appraisal of the manufacturer's NMA. In general the overall methods in the NMA appeared to be of reasonable quality, but in those sections of results that the ERG had sufficient time to check there were errors that may be symptomatic of more general deficiencies. The clarity of NMA reporting was less good.

See Section 3 in the ERG report for additional information about clinical effectiveness.

Model Implementation Cross-check

The Empagliflozin Cost Effectiveness Model (ECEM) consists of:

- An Excel front end that acts as a store of parameter values
- Visual basic (VB) code that forms the actual model
- An Excel back end for the outputting of the visual basic results

Model Structure

The main model structure is drawn from the equations of the UK Prospective Diabetes Study (UKPDS 68). See Figure 17 in the ERG report for an ECEM structure. The ECEM is a patient level state transition model. That is to say it models individual patients' transitions between health states using a fixed cycle length. The cycle length of the model is six months. This is apparently mainly to enable patients to switch treatments at the six month point. Note that the UKPDS 68 estimates annual probabilities of transitions. The calculation of the six monthly probabilities of the ECEM is not entirely in line with the calculation of the annual probabilities of the UKPDS 68, but the two are closely aligned.

The time horizon of the model is 40 years, the perspective is that of the National Health Service (NHS) and Personal Social Services (PSS) for costs and patients for benefits, and costs and benefits are discounted at an annual 3.5%.

The Economic Model

Three comparisons are made:

Dual therapy:

- Empagliflozin 10 mg and 25 mg plus metformin versus sitagliptin 100 mg plus metformin
- Empagliflozin 10 mg and 25 mg plus metformin versus dapagliflozin 10 mg plus metformin
- Empagliflozin 10 mg and 25 mg plus metformin versus canagliflozin 100 mg and 300 mg plus metformin

Triple therapy:

- Empagliflozin 10 mg and 25 mg plus metformin plus SU versus metformin plus SU plus sitagliptin 100 mg
- Empagliflozin 10 mg and 25 mg plus metformin plus SU versus metformin plus SU plus dapagliflozin 10 mg
- Empagliflozin 10 mg and 25 mg plus metformin plus SU versus metformin plus SU plus canagliflozin 100 mg and 300 mg

Add-ons to insulin regimens:

- Empagliflozin 10 mg and 25 mg versus metformin plus sitagliptin 100 mg
- Empagliflozin 10 mg and 25 mg versus metformin plus dapagliflozin 10 mg
- Empagliflozin 10 mg and 25 mg versus metformin plus canagliflozin 100 mg and 300 mg

See Section 4 in the ERG report and the MS (see the "Availability of Companion Documents" field) for additional information on the economic model.

Cost-effectiveness

Summary and Critique of Manufacturer Submitted Economic Evaluation by the ERG

Cost-effectiveness Analysis (CEA)

The CEA uses a stochastic micro-simulation (the ECEM) to estimate the cost-effectiveness of empagliflozin compared with SU, pioglitazone, sitagliptin, dapagliflozin, canagliflozin and insulin in adults with type 2 diabetes mellitus.

Comparison of Economic Submission with NICE Reference Case

See Table 29 in the ERG report for NICE reference case checklist.

See Section 5 of the ERG report and the MS for additional information on the cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee discussed the new cost-effectiveness model the company had provided. It noted that the new model was validated and had been used for previous National Institute for Health and Care Excellence (NICE) technology appraisal guidance.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee discussed the new cost-effectiveness model the company had provided. It noted that the new model was validated and had been used for previous NICE technology appraisal guidance. The Committee concluded that the new model and associated results provided a suitable basis for decision-making.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

Not applicable

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

Not applicable

What Are the Key Drivers of Cost-effectiveness?

There were no specific Committee considerations on the key drivers of cost effectiveness.

Most Likely Cost-effectiveness Estimate (Given as an Incremental Cost-effectiveness Ratio [ICER])

The Committee concluded that the very small differences in costs and quality-adjusted life years (QALYs) between empagliflozin (10 mg and 25

mg) and its key comparators showed that empagliflozin was a cost-effective use of National Health Service resources as dual therapy in combination with metformin, triple therapy in combination with metformin and either a sulfonylurea or a thiazolidinedione, and as an add-on treatment to insulin.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of empagliflozin and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from four randomised controlled trials (RCTs). For cost-effectiveness, the Appraisal Committee considered the manufacturer's economic model.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of empagliflozin in combination therapy for treating type 2 diabetes

Potential Harms

The summary of product characteristics states the following adverse reactions for empagliflozin as the most commonly reported: hypoglycaemia in combination with insulin or a sulfonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (that is, urinary frequency).

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has type 2 diabetes and the doctor responsible for their care thinks that empagliflozin is the right treatment, it should be available for use, in line with NICE's recommendations.
- NICE has developed tools to help organisations put this guidance into practice (listed below).
    - A costing statement explaining the resource impact of this guidance.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Empagliflozin in combination therapy for treating type 2 diabetes. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 44 p. (Technology appraisal guidance; no. 336).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Mar

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Empagliflozin in combination therapy for treating type 2 diabetes. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 4 p. (Technology appraisal guidance; no. 336). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Shyangdan D, Jacob R, Connock C, Johnston R, Cummins E, Waugh N. Empagliflozin for the treatment of type 2 diabetes: a single technology assessment. Warwick (UK): Warwick Evidence; 2014 Jul. 165 p. Electronic copies: Available from the NICE Web site .
- Empagliflozin for the treatment of type 2 diabetes mellitus (T2DM). Single technology appraisal. Manufacturer's submission. Boehringer Ingelheim Ltd.; 2014 Apr. 455 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Empagliflozin in combination therapy for treating type 2 diabetes. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Mar. 3 p. (Technology appraisal guidance; no. 336). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download as a Kindle or EPUB ebook from the NICE Web site . Also available in Welsh from the NICE Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 11, 2015. This summary was updated by ECRI Institute on December 11, 2015 following the U.S. Food and Drug Administration advisory on SGLT2 Inhibitors. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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